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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,826	07/10/2006	Markus Linder	0365-0662PUS1	5038
2292 7590 08/06/2009 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747				
EXAMINER MOHAMED, ABDEL A				
ART UNIT		PAPER NUMBER		
1654				
NOTIFICATION DATE		DELIVERY MODE		
08/06/2009		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary

Application No.

10/563,826

Applicant(s)

LINDER ET AL.

Examiner

Abdel A. Mohamed

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 June 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2 and 5-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-7 and 9-13 is/are rejected.
- 7) ☐ Claim(s) 8 and 14 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 June 2009 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

ACKNOWLEDGMENT TO AMENDMENT, DRAWINGS, REMARKS AND STATUS OF THE CLAIMS

1. The amendment to the claims, drawings and remarks filed 06/22/09 and 06/26/09, respectively are acknowledged, entered and considered. In view of Applicant's request claims 1, 2, 5-7 and 11 have been amended, claims 3 and 4 have been canceled and claims 12-14 have been added. Claims 1, 2 and 5-14 are now pending in the application. The objection to the claims and the rejection under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment, cancellation and remarks filed 06/22/09.

NEW GROUND OF REJECTION

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-7 and 9-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cleaving a protein or a peptide at a specific site wherein the method comprises the steps of constructing at a predetermined cleavage site of the protein or peptide an amino acid sequence of 2 to 20

amino acids, wherein the amino acid sequence comprises His His or repeats thereof of His₆-His₈ (i.e., SEQ ID NOS:29 and 30), and said amino acid sequence is cleavable in the presence of transitional metal of Cu or Co, said amino acid sequence does not exist naturally in the protein or peptide to be cleaved; and allowing said protein or peptide to react with the transitional metal in a buffer to cleave said protein or peptide; said buffer further comprising a reducing or oxidizing agent or agents, wherein the agents are ascorbate or hydrogen peroxide or both, does not reasonably provide enablement for a method of cleaving a protein or a peptide at a specific site wherein the method comprises the steps of constructing at a predetermined cleavage site of the protein or peptide an amino acid sequence of 2 to 20 amino acids, wherein the amino acid sequence comprises X₁ X₁ or repeats thereof, wherein X₁ is His and said amino acid sequence is cleavable in the presence of free metal ions as recited in claims 7 and 14, said amino acid sequence does not exist naturally in the protein or peptide to be cleaved; and allowing said protein or peptide to react with the metal ion in a buffer, said buffer further comprising a reducing or oxidizing agent or agents as claimed in claims 1, 2, 5-7 and 9-13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not enable a method for cleaving protein or peptide at a specific site of an amino acid sequence comprising His₂ or His₄ cleavable in the presence of free ions of Ni, Fe, Mn, Cd, Pd, Rh, Ru, Pt, Cr and Zn in a buffer, said buffer further comprising a reducing or oxidizing agent or agents as broadly claimed in

claims 1, 2, 5-7 and 9-13 because there are no working examples or data cited in the instant specification to support such claims. The instant specification on Example 3 discloses cleavage of a linker containing six consecutive histidines *versus* control which resulted the protein with histidines in the linker is cleaved, whereas the control protein remains uncleaved (See also Figure 10). Example 4 also discloses the effect of Cu wherein the addition of Cu enhances the cleavage of protein with His₆, whereas protein without the cleavage site (e.g., Gly) is not cleaved (See also Figure 11). Example 5 and Figure 12 demonstrate the effect of different ions such as Cu, Ni, Fe, Zn and Co in which Cu and Co showed cleavage of fusion protein containing His₆ while the other ions did not. Example 9 and Figure 17 disclose the effect of linker composition, wherein His₆ in the linker is cleaved more efficiently than linker containing two or four histidines. Similar results were obtained in Example 10 and Figure 18, wherein a more efficient cleavage into linker composition was seen with the His₃ and His₆ repeats containing segments. Further, the instant specification on page 11, lines 18-24 states that in the experimental part of the invention is shown that His-residues in a peptide segment promote cleavage of the segment in the presence of for example Cu ions and other reagents such as ascorbate and hydrogen peroxide. As shown in the examples (example 9) two adjacent His residues already causes cleavage. Increasing this number to 4, 6, or 8 increases the reactivity of the segment (Example 9). Surprisingly, a segment with six His residues that have some other residue between each of His residues is also very reactive, and may be even more even reactive than six consecutive His residues (example 10).

Similarly, the reference of Andberg et al (Protein Science, Vol. 16, pp. 1751-1761, 2007) of which 4 of the inventors, namely Markus Linder, Jussi Jannti, Hans Soderlund and Ari Koskinen are co-authors of this reference which shows cleavage of recombinant proteins at poly-His sequences by Co and Cu (See e.g., the Title). Also, the abstract states that in this work we show by gel electrophoresis and mass spectroscopy that salts of Co and Cu can be used to cleave fusion proteins specifically at sites where sequences of His residues have been introduced by protein engineering. The His residues could be either consecutive or spaced with other amino acids in between. The cleavage reaction required the presence of low concentrations of ascorbate and in the case of Cu also hydrogen peroxide. On page 1752, the reference shows the strategy of using various chelates of metal ions of metals such as Ce, Co, Cu, Mo, Ni, Pd, Pt, Zn and Zr. Further, using Fe did not cause any reaction, but very clear reactions were obtained by the addition of Cu or Co. Similarly, Figure 4 shows no effect of treatment with Fe, Ni, and Zn while some effect can be seen with Co and the largest with Cu. Also, the number of His residues in the linker region clearly affected the cleavage reaction, wherein adding more than six residues only slightly improved the cleavage, as was demonstrated with fusion proteins containing eight or ten His residues (See e.g., page 1758, left column and Figure 8).

Therefore, in view of the above, there is no data or activity in the instant specification showing the use of a method for cleaving protein or peptide at a specific site of an amino acid sequence comprising His₂ or His₄ cleavable in the presence of free ions of Ni, Fe, Mn, Cd, Pd, Rh, Ru, Pt, Cr and Zn in a buffer, said buffer further

comprising a reducing or oxidizing agent or agents as broadly claimed in claims 1, 2, 5-7 and 9-13. Moreover, without guidance, the use of any protein or peptide in general in a method of cleavage at a specific site comprising X_1 X_1 or repeats thereof wherein X_1 is His cleavable in the presence of free metal ions as claimed in claims 7 and 14, and allowing said protein or peptide react with the metal ion in a buffer having a reducing or oxidizing agent or agents in general in which the effects of cleavage are unknown for the reasons discussed above, and as such, when this variable is added, the claimed invention becomes little more than conjecture and is not workable in view of Applicant's acknowledgement and/or admission in the instant specification as shown above and in view of Applicant's work which was published after filing the instant invention as discussed above, and as such, the experimentation left to those skilled in the art is unnecessary and improperly, extensive and undue. See *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d, 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Therefore, the scope of the instantly claimed invention is speculative in claiming a method of cleaving a protein or a peptide at a specific site wherein the method comprises the steps of constructing at a predetermined cleavage site of the protein or peptide an amino acid sequence of 2 to 20 amino acids, wherein the amino acid sequence comprises X_1 X_1 or repeats thereof, wherein X_1 is His and said amino acid sequence is cleavable in the presence of free metal ions as recited in claims 7 and 14, said amino acid sequence does not exist naturally in the protein or peptide to be cleaved; and allowing said protein or peptide to react with the metal ion in a buffer, said

buffer further comprising a reducing or oxidizing agent or agents as claimed in claims 1, 2, 5-7 and 9-13 for the reasons discussed above.

Furthermore, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, *id.* at 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, without guidance through working example(s), one of ordinary skill in the art would not predict from the method of cleaving a protein or a peptide at a specific site wherein the method comprises the steps of constructing at a predetermined cleavage site of the protein or peptide an amino acid sequence of 2 to 20 amino acids, wherein the amino acid sequence comprises His His or repeats thereof of His₆-His₈ (i.e.,

SEQ ID NOS:29 and 30), and said amino acid sequence is cleavable in the presence of transitional metal of Cu or Co, said amino acid sequence does not exist naturally in the protein or peptide to be cleaved; and allowing said protein or peptide to react with the transitional metal in a buffer to cleave said protein or peptide; said buffer further comprising a reducing or oxidizing agent or agents, wherein the agents are ascorbate or hydrogen peroxide or both disclosed in the instant specification to substitute and/or modify any other transitional metal claimed in claims 7 and 14 and use of His₂ or His₄ and use of agents such as dithiothreitol in the manner claimed in the instant invention in view of Applicant's admission as recited in the instant specification and as shown above and in view of Applicant's publication (i.e., The Andberg reference) and in view for the reasons discussed above. Thus, the specification does not enable any person skilled in the art to which it pertains, or which is most nearly connected, to use the invention commensurate in scope with the claims. In the express absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention.

CONCLUSION AND FUTURE CORRESPONDENCE

3. Claims 8 and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mohamed/A. A. M./
Examiner, Art Unit 1654

/JON P WEBER/
Supervisory Patent Examiner, Art Unit 1657